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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/797,903	03/10/2004	**Yuji Yamamoto**	25142-0002001	3373

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EXAMINER	
PAGONAKIS, ANNA	
ART UNIT	**PAPER NUMBER**
1628	

NOTIFICATION DATE	DELIVERY MODE
04/01/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/797,903	YAMAMOTO ET AL.	
	Examiner	Art Unit	
	ANNA PAGONAKIS	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,14,16-18 and 20-37* is/are pending in the application.

4a) Of the above claim(s) *16,21,28 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,14,17,18,20,22-27,29-34,36 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 sheet; 11/18/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 1/20/2010 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

As reflected by the attached, completed copy form PTO/SB/08A (one page total), the Examiner has considered the cited references.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

I do not agree with this rejection. Applicants have adequately described the genus. Do you have a problem with the enablement, e.g., scope? If not, set up the patentability conference.

Deleted the written description and wrote a scope of enablement below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 14, 17-18, 20, 22-27, 29-34, 36 and 37 are rejected under 35 U.S.C. § 112, first paragraph, because while the specification, while enabling for the administration of Compound 1, the elected compound, to inhibit *in vivo* phosphorylation of c-kit and thereby inhibiting the activity of c-Kit kinase in an H-526, does not reasonably provide enablement for the asserted utility for the entirety of the Markush-type Formula (I). The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

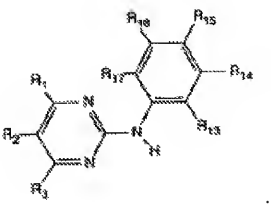
In particular, the specification and claims as originally filed fail to provide adequate written description for the *genus of compounds represented by formula (I)* for the treatment of cancer comprising determining if the patient's cancer expresses c-Kit kinase or a mutant c-Kit kinase.

As stated in the MPEP 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'." The court (*In re Wands*, 8 USPQ2d 1400 (1988)) established the following factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph:

1) The nature of the invention – involves compounds represented by general formula (I) drawn to a method for treating a cancer in a patient comprising determining if the patient's cancer expresses c-Kit kinase or a mutant c-Kit kinase; if the cancer is determined to express c-Kit kinase or a mutant c-Kit kinase.

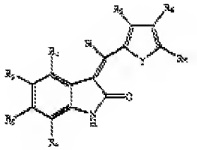
2) The state of the prior art - the pharmacological art requires the screening of potential drug candidates *in vitro* and *in vivo* to determine if the drug candidates exhibit the desired pharmacological activities.

In this case, the prior art recognizes the treatment of interstitial cystitis and inhibition of mast cell proliferation with the use of c-kit kinase inhibitors having the core structure: (WO 03/024386; abstract



and page 4, lines 16-19; page 6, line 16) .

Further the prior art teaches the inhibition of cell proliferative disorders with administration of known c-kit kinase inhibitors having the core structure (U.S. 2002/0010203; paragraph [0039] and [0003]):



3) The predictability or unpredictability of the art - the pharmaceutical art is unpredictable and requires each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 24 (CCPA 1970). As stated in MPEP 2164.02: "'correlation' as used herein refers to the relationship between *in vitro* and *in vivo* animal model assays and a disclosed or a claimed method of use . . . if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." The more unpredictable an area is the more specific disclosure is necessary in order to satisfy the statute.

Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonably degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore, it is well known in the art that cultured cells, over a period of time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York., p4) teach that it is recognized in the art that there are many differences between cultured cells and

counterparts in vivo. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissues are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4., see Differences in Vitro). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is note. Yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been scientific characteristics different form those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host-tumor and cell-cell interactions.

In addition, the treatment of cancer is at most unpredictable as underscored by Gura (Science, v278, 1997, pp. 1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed since forma screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, column one) wherein the fundamental problem in drug discovery for cancer is that the model systems are not.

4) The amount of direction or guidance presented –

Applicant provides an example of the administration of Compound 1, the elected compound, to

inhibit *in vivo* phosphorylation of c-kit and thereby inhibiting the activity of c-Kit kinase in an H-526 tumor (paragraph [0061] of the specification).

5) The presence or absence of working examples - The instant specification discloses compounds 1, 2, 3 and 4 inhibited the cell proliferation stimulated by SCF and that these compounds were *considered* to possess c-kit kinase inhibitory activity *in vitro* (emphasis added). Thus, while the specification provides an example of inhibiting in vivo phosphorylation using the elected compound, the specification appears to be silent on any correlation between the in vitro testing and in vivo success for the full breadth of the claims. As such, if there is no correlation then the examples do not constitute working examples. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention.

6) The breadth of the claims – is incommensurate in scope with the disclosure. The Markush-type formula of claim 1 encompasses several substituents (R1, R2, R3 and R4), each of which consisting of a plethora of variables. The instant specification discloses the *in vitro* inhibition of cell proliferation with administration of Compounds 1, 2, 3 and 4. Further, the specification Applicant provides an example of the administration of Compound 1, the elected compound, to inhibit *in vivo* phosphorylation of c-kit and thereby inhibiting the activity of c-Kit kinase in H-526 tumor.

7) The quantity of experimentation necessary – It remains that Applicant has failed to provide any exemplary, let alone delimiting description of the genus of compounds in formula I for the treatment of cancer and further the inhibition of both c-kit kinase and mutant c-kit kinase.

8) The level of skill in the art - the level of ordinary skill in the art may be found by inquiring into: (1) the type of problems encountered in the art; (2) prior art solutions to those problems; (3) the

rapidity with which innovations are made; (4) the sophistication of the technology; and (5) the education level of active workers in the field. *Custom Accessories, Inc.*, 807 F.2d at 962. All of those factors may not be present in every case, and one or more of them may predominate. *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 696 (Fed.Cir.1983).

Conclusion – although the level of skill for an ordinary person in the art is high, the skilled artisan would not be able to make and use the instant invention without undue experimentation due to the breadth of claims, the unpredictability of the art, the lack of guidance or direction from the disclosure, and the lack of working examples.

The Examiner suggests an amendment to the instant claims such that formula of claim 12 is limited to the administration of Compound 1, the elected compound, to inhibit c-kit kinase and thereby in an H-526 tumor.

Conclusion

No claim is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 9am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642